Basic science

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GENERAL CONSIDERATIONS

New knowledge continues to be needed, even in the face of incomplete application of what has already been learned, in order to have technologies better adapted to the needs and circumstances of the countries other than where they were developed. There is also the unmistakable fact of the revolutionary push of new science and new technologies – outstandingly so in fields like bio-technology, electronics, computers and communications, that simply cannot be overlooked in the development of the most effective modalities for health care.

But the speed of growth of knowledge in science and technology means that there is a great need for careful selection, by developing countries, of the available technologies. Here the metaphor of 'receptor site' in a developing country is appropriate: for well informed, dynamic, and critical assessment of the kind of technologies that are available or are often thrust in great profusion towards the developing countries. And indeed there are many hazards of industrialization that require particular attention in order to forefend environmental disasters like those associated with air pollution, or radioactive or chemical accidents, in a variety of places. So even the most advanced technologies cannot simply be purchased over the counter, in a turnkey fashion. They must be dynamically received, with an alert constituency capable of adapting them optimally to the needs of the recipients.

An outstanding example of the requirements for the adaptation of technology is still with us in the field of vaccines. There are millions of children and adults throughout the world who die or suffer needlessly

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* Professor Lederberg chaired the Colloquium's session on Basic Science. The presentation *General Considerations* is adapted from a previous paper of his in the WHO publication *Research Strategy for Health*. The presentations on the *Current Situation* and *Discussion* are a synthesis of the Colloquium's deliberations. The annexed articles by Professor Lederberg are included for the purpose of presenting a more complete representation of the role of the DNA technologies in present day science and medical care.

over the years, where infectious disease is known to be preventable by the administration of vaccines that have already been developed.

But in many cases, these vaccines are poorly adapted to the requirements of developing countries. If they require a cold chain, which is typically the case, this is no problem in an advanced or industrialized setting; but it could be an insuperable obstacle to their effective use in remote rural areas. And yet, physical chemists could find very exciting scientific challenges in devising ways to ensure the thermostability of protein vaccines, even in the face of great external insult; there has simply been no requirement for that as part of the specifications for vaccines in the developed world. A vaccine that needs to be administered on repeated occasions, which is typical of many vaccines, poses no problems in settings where families can go to their personal paediatrician every two or three months, and receive three or four inoculations over a period of a year. This is obviously an inappropriate model for health care in many other settings, and yet those are the vaccines that are available at the present time.

But even at its best, science can sometimes be wrong; it should not be understood as being a reservoir of fixed and enduring 'revealed knowledge' – unalterable, and totally reliable in all circumstances.

It was a third world scientist, S.N. De who set things right about cholera toxin, some 35 years ago: fundamental research on toxins had been misdirected for a very long period of time, based on confounding research in microbiology and a concept of toxins that was quite appropriate for tetanus, diphtheria, staphylococcus and pertussis, but inappropriate for cholera. The cholera toxin does not kill by the same kinds of cell toxic mechanisms as apply to these other entities, and an approach that was too close to the laboratory, and too far from the field, was a tragic misdirection of scientific development. Only effective collaboration between the sites of disease and the laboratory studies needed to substantiate them has made it possible to correct that situation. Many other such examples could be mentioned.

Communicable diseases transcend political boundaries. There is an urgent need, which is only dramatized by the AIDS pandemic (who can believe that this is the first or last example of that manifestation of viral evolution, although many policies are directed as if it is a unique circumstance?), for sentinels of local surveillance that have the capacity to detect new and emerging viruses, newly drug-resistant parasites, evolving vectors, and new contacts with zoonoses, in order to contain outbreaks of communicable disease and deal with them most effectively at their early stages, before they become a metastatic cancer that engulfs the globe.

Scientists in the developing countries have both the personal right and the national necessity to participate in the global progress of technology and in the fellowship of international science, to permit the flowering of genius, and to permit the most effective contributions to economic and technical development of their own countries.

Molecular genetics has moved from the laboratory prototype of the understanding of rare diseases where a single gene determines the presence or absence of disease. From these very rare circumstances, with a few exceptions (notably thalassenia and sickle cell disease), of limited public health significance, we are moving now into the application of that kind of science to the much broader problems of predisposition to more common diseases. These vary from well established prototypes in cardiovascular disease, to a few forms of cancer and perhaps most exciting of all, the portent of application to severe behavioural disorders. Starting with Huntington's disease there is progress in the understanding of bipolar affective disorders, depression and schizophrenia, where we have a very involved etiology and where the genetic component may be the one that enables us to unravel a more complicated situation, even if the genetic component is not always of primary significance. The cardiovascular disease situation is a wonderful example of this, in that the molecular genetics study of rare syndromes has opened up our understanding of one of the most common group of diseases.

Monoclonal antibodies have provided indispensable new reagents for diagnosis, and in a few cases for therapeutic applications. And now we see them being developed not only in mice and in human lymphoid cells, but even in bacteria, and by bacteriophages that give still more amenable approaches to their control and manipulation.

In neurobiology our understanding of the ever increasing panoply of neuro-transmitters has given us new insights to the action of psychotropic drugs and also opened our eyes to neurotoxins of dietary origin and how they may be important in significant disease syndromes in special settings. Recombinant DNA vaccines are no longer dreams of the future; they already play a pre-eminent role in hepatitis vaccines, but that is only the first example; there will be a long series of greatly improved specific vaccines for a variety of circumstances.

We have new findings in cancer diagnosis, in therapy; we have new approaches for environmental monitoring and the assessment and response to ecological threats; new materials for prostheses; new approaches to drug design. All of these findings should be expanded and developed in the context of well thought out health systems, guided by

health systems research, as has already been noted. It is not just a matter of passively waiting for the design of the system and fitting research into it; the potentialities of research and new technology have also to be part of the design of the health care system, that can help support the kind of rigour and application of quantitative methodology which is absolutely essential for all research. Furthermore, new technologies can bring in new information systems to help support the rational integration of the entire health system – and indeed of the 'health cum economic' system.

All of these advances will become possible only if a full partnership is established between the developed and the developing countries: in the human resources, in the personal interactions of people with different skills, coming from different settings, and seeking the application of science in most parts of the world.

CURRENT SITUATION

The development of the DNA technologies represents the most important and significant advances in the basic sciences relative to health. They have enabled the development of new and safer vaccines, medicines and therapeutic agents; highly sensitive and specific diagnostic tests and procedures; the large scale production of existing biological substances; and an understanding of normal life and disease processes. These developments and the commercial availability of required reagents makes the application of the technologies globally possible.

Currently the following technologies are amongst those being applied to research and investigation, and the treatment or control of many major health problems:

- DNA cloning
- DNA sequencing
- protein sequencing and *in vitro* assembly
- polynucleotide synthesis
- polymorphism detection and *in vitro* hybridization
- Polymerase Chain Reaction (PCR)
- gene splicing
- transgenics
- transplants
- RNA-ribozymes
- monoclonal antibodies
- phage presentation

Investigations, Epidemiology

Major interest is in molecular epidemiology and genetics and the Human Genome Project. Studies of significance are those relating to the epidemiology of genetic diseases and defects and the common diseases with genetic predisposition. Other examples of interest in application of this knowledge are in biological psychiatry, mental disorders, gene therapy, male fertility and family planning, pathological ageing and the relationship of HIV strains.

Vaccine research is centred around the development of vaccines for cholera and other diarrhoeal diseases, malaria, schistosomiasis, tuberculosis, AIDS and other infectious diseases. Vaccine technology currently is focussed on the application of subunits and conjugates; altered pathogens; bacterial and viral vectors; microspheres, attenuated viruses and naked DNA. Research is also ongoing for a cancer vaccine. At this time consideration for this vaccine is strictly for therapeutic application. The development of heat stable and one shot vaccines are research targets of great importance.

Other investigative work is in the continued development of the biological control of vectors, transgenics and organ transplants.

Diagnostics, Case Detection

Highly sensitive and specific diagnostic tests have been made possible by the DNA technologies. Monoclonal antibodies, defined and purified antigens, nucleic acid probes and PCR now form the basis for many standard diagnostic techniques. Based on these technologies diagnostic kits are available for use in areas which include many of the communicable diseases, AIDS, the zoonoses and food safety. They have also led to the development of pocket test kits and dipsticks for field use in tropical disease, sexually transmitted disease, cholera and other disease control programmes.

The understanding of molecular genetics and the application of genetic markers are making it possible to predict whether a person has or will develop a genetic disease or to detect common disorders with a genetic predisposition. Examples of the application of these techniques include control of haemoglobinopathies, detection of hereditary and chronic diseases, fertility regulation, HIV and tropical disease control.

Treatment

The major thrust in disease control has been in the development of new vaccines or the improvement of existing vaccines with the Hepatitis B vaccine being the initial success. More recently two new cholera

vaccines have been licensed in some countries. Target vaccines include those for diseases which are major causes of mortality of children in developing countries. Vaccines for other than communicable diseases include an anti-fertility vaccine and a rabies vaccine.

The technology has also led to the development of new drugs and therapeutic agents such as insulin and the human growth hormone. Recent work includes effective drugs for leprosy and onchocerciasis.

The treatment and prevention of genetic, hereditary and related diseases are receiving increased attention. The developments in basic genetic concepts, somatic gene therapy and defective gene replacement are making possible the treatment of many of these noncommunicable diseases.

Nutrition

Genetic manipulation of plants has increased yield and food production. Further, the nutritional quality of the product can be improved, e.g. increasing the content of essential amino acids in plants or rearing cattle that yield low fat meat.

DISCUSSION

In spite of the high level of activity in research and development in the DNA technologies, the products needed by the most vulnerable in the developing countries and poorest populations are either not available or are not affordable.

This is due to several factors. Initial research and the following product development are expensive, thus industry incurs extensive costs before the product is placed on the market. As industry must make a profit it tends first to concentrate on those products which are profitable. In the health care industries these tend to be therapeutic products rather than vaccines, or those vaccines which are most required by the poorest populations. High cost is also due to governmental regulations, often restrictive, pertaining to the DNA technologies. This is further compounded by the fact that international harmonization of such regulations has not occurred. Another restriction to research and product development is that of patent rights. Lengthy periods of time are required for obtaining patents and considerable legal expenses are entailed. Ethically such factors should not interfere with critical research and development and the group expressed the group hope that WHO and the ACHR could make recommendations on how to alleviate the problem.

Discussion also related to the possibility of developing the means for basic research and or product development in those countries where they are needed the most. This requires considerable infrastructure development but such has paid off in the advanced developing countries in Asia and Latin America.

In summary, it was noted that products produced by DNA technology bear the burden of heavy fixed development costs, and that affordable products are required. The growing participation of developing countries may help to ameliorate this obstacle, taking note of encouragement from organizations like the International Center for Genetic Engineering and Biotechnology (ICGEB: Trieste and New Delhi). It was also stressed that any applications of DNA technology pertaining to humans should be conducted with respect to privacy and ethical conduct or else in many cases be completely averted.

It was agreed that:

- Efforts should continue to explore and expand the applications in diagnosis, therapy, prevention and investigation of pathogenesis of diseases, particularly as they apply to infections, heart disease, autoimmune disorders, cancer, ageing, mental disorders, family planing and food production. Molecular biology technology also has enormous potential in the manufacture of valuable protein products (thrombopoeitin, vaccines), in production of transgenic animals, transplants, anti-viral agents and in cellular regulatory processes.
- Ethical aspects of somatic gene therapy have raised no new issues, but germ line therapy should be kept on hold until its ramifications are more deeply understood and widely accepted. The WHO and CIOMS should continue in cooperation with other international organizations to explore international agreement on a code of ethics in molecular biology especially on the human genome project.

Review articles by Professor Lederberg for further reading:

- Emerging Infections: Microbial Threats to Health. *Trends-Microbiol.,* May, 1993, 1 (2):43-44.
- The Transformation of Genetics by DNA. *Genetics,* February, 1994, 136 (2):423-426.
- An Early History of Gene Transfer and Therapy. *Hum-Gen-Ther.,* April, 1994, 5 (4):469-480.

The following review articles by Professor Lederberg are annexed:

- Medical Science, Infectious Diseases, and the Unity of Humankind. *JAMA,* August 5, 1988, 260 (5): 684-685.
- The Interface of Science and Medicine. *Mt-Sainai-J-Med.,* October, 1992, 59 (5): 380-383.
- What the Double Helix (1953) has Meant for Basic Biomedical Science: A Personal Commentary. *JAMA,* April 21, 1993, 269 (15): 1981-1985.